canceled those claims and added new claims 98 to 128. These amendments have been made to better define the invention. Support for new claim 98 may be found in now canceled claims 74 and 86, as well as on page 8 of the Specification. Support for new claims 99 to 113 may be found in now canceled claims 74 to 79 and claims 86 to 91, and pages 7-8 and 9-14 of the application. New claims 114 to 128 are supported by the application as originally filed, including claims 2 to 10; claims 16 to 18; claims 22 and 23; and claims 30 to 32. No new matter is added by these amendments.

Election/Restriction Requirement

In paragraphs 6 to 14 of the Office Action, the Examiner set forth two restriction requirements, which were communicated to the undersigned during the October 11, 2000 telephone interview, and to which Applicants provided a verbal response. First, the Examiner divided the claims into two groups, alleging that the inventions in those groups are distinct from each other. One of said groups comprises claims 74-84 and 86-96, directed to a method of identifying a compound having a selected property of interest in library of compounds; and the other comprises claims 85 and 97, directed to an apparatus for performing such a method.

The Examiner also required species election, requesting that Applicants elect one species of "compound, " "selected property of interest," and "array" for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held allowable. The Examiner also requested that Applicants, in addition to identifying the species elected, list all claims readable thereon.

In response to the first restriction requirement, Applicants verbally elected without traverse the claims of Group I, directed to a method of identifying a compound having a selected property of interest, for further prosecution. Applicants now confirm that election, and note that all the apparatus claims have been canceled

In response to the second restriction requirement, Applicants elect oligopeptide as the compound and "binding to a probe" as the property. Applicants note that during the verbal communication, the undersigned has mistakenly communicated to the Examiner that the compound species selected is oligonucleotide, instead of oligopeptide. Applicants apologize for the inconvenience caused by this inadvertent error, and respectfully request that the Examiner permit the right selection to be made for the compound species. As for the claims directed to an array, they have now been canceled without prejudice. It is Applicants' understanding, however, that once the generic claims are found allowable, claims directed to additional species (e.g., where the compound in the library comprises an oligonucleotide, oligosaccharide, etc) may be allowed along with the generic claims. Claims 98 to 113 and 121 to 128 are generic claims.

35 U.S.C. §112, First and Second Paragraph, Rejections

The Examiner objected to the application as (i) not containing specific reference to the prior applications in the first sentence of the specification; (ii) for incorporating the subject matter of the provisional application; and (iii) for use of trademarks. Applicants have amended the application in response to the first two of these objections by putting in the information about the prior applications, and replacing the provisional application number with the U.S. Serial Number of the corresponding application. As for the trademark related objections, words pointed out by the Examiner ("ZEIS UEM," "ALDRICH," and "AMERSHAM" do not identify a product and thus are not trademarks as defined by MPEP 608.01 (v), but are just the names of companies from which the material specified may be obtained. Accordingly, Applicants respectfully request reconsideration of those objections.

The Examiner rejected claims 76-78 and 89-91 under 35 U.S.C. §112, first paragraph, alleging that the fluorophore dyes of specific structure and chemical names set forth in those claims were not present in the application as originally filed, thus are not supported by said application. Based on these allegations, the Examiner stated that the filing date for these claims is

the filing date of the instant U.S. application. See paragraphs 16 and 20 of the Office Action. The Examiner also referred to the second chemical structure of claim 78 and the third chemical structure of claim 91, stating that those dyes should have a carboxyl group on the benzene ring. See page 8 of the Office Action. Applicants respectfully traverse these rejections.

Claims 104 to 106 correspond to now canceled claims 76-78 and 89-91, and recite the dyes set forth in those canceled claims. Applicants respectfully note that the dyes of these claims correspond to those found in claims 20 to 21, which were originally present in the originally filed PCT Application No. PCT/US98/10719. Applicants also direct the Examiner's attention to pages 15 to 17 of the Specification. In the originally filed claims, these dyes were referred to by their trademarks. Later these were replaced with their corresponding chemical and structural names in response to the Examiner's objections to the use of trademarks. Specifically, in a response to the Written Opinion of April 28, 1999, in which the Examiner objected to the use of trademarks for referring to specific fluorophore dyes, Applicants pointed out that these dyes were commonly referred to by their trademark names in practice because of the complexity of their chemical names and structures, and because those trademarks uniquely identify each dye product, thus are specific indicators of structure, and not merely the source. Even so, in order to expedite the prosecution of the application, Applicants amended the claims, substituting the trademark names of those dyes with corresponding chemical names and chemical structures. Also submitted was a list setting forth the dyes referred to in the original application by their trademark names along with their corresponding substituted chemical names or structures. See pages 9-10 of the June 28, 1999 Response to the Written Opinion, and Exhibit F of the response. In view of the foregoing, Applicants respectfully maintain that the claims 104 and 106 are fully supported by the original application and entitled to its filing date. As for the two particular chemical structures referred to by the Examiner, Applicants state that those were the structures provided by the manufacturer of the dyes, and once again refer to the list that was submitted as Exhibit F of the June 28, 1999 Response.

In paragraph 23 of the Office Action, claims 74-81, 83-84, 86-93 and 95-96 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Specifically, the Examiner alleged that claims 74 and 86 are indefinite, because the phrase "wherein fluorophore tag represents a bit binary code, and comprises zero, one or more than one fluorescent dye" is not clear. The Examiner also requested clarification of step (d) in which the M batches are recombined. In addition, referring to claim 74, the Examiner alleged as follows: (i) the claim recited "performing an assay capable of indicating," but the specification does not specifically teach an assay in which the compound in the library has the property of interest; (ii) the claim recites that the assay is performed while the compound is either bound or cleaved from the solid support, whereas the tag is to be attached to the solid support. Since the tag may be attached to the component of the solid support, the Examiner stated, it is unclear how that tag may still be bound to the solid support when the component is cleaved. Applicants respectfully traverse these rejections.

Claims 98 to 128 provide that a combinatorial compound library is synthesized on solid supports by a series of reaction steps in which the solid support is reacted with a component of the compound. The identity of the component is encoded by attaching a spectrally distinguishable fluorophore tag that is uniquely associated with each component. The claims recite that the fluorophore tag "represents a bit of a binary code and comprises zero, one, or more than one fluorescent dye(s)." Applicants respectfully maintain that this phrase is not indefinite. The term "a bit of binary code" indicates that the encoding step of the claims involves a binary coding strategy. The word "bit" is a short-hand for binary digit, that is bits are the digits of a binary code, namely, 0 and 1, or any physical representation thereof. In an encoding strategy where identifier tags (e.g., spectrally distinguishable fluorophore tags of the subject application) are used in a binary coding scheme, the absence of such tag (e.g., the fluorophore dye component of the tag in the subject application), as well as its presence, is used as an indicator of the identity of the compound. Such a scheme corresponds to a known standard method of storing digital information and is analogous to bar codes. In the context of chemical libraries, Ohlmeyer et al., PNAS, volume 90, pp. 10922-10926 (1993) provides an example of the use of a strategy to

encode a combinatorial library of compounds, and refers to the "bits" of binary code. See page 10923, right column, last paragraph, to page 10924, left column. Although Olhmeyer et al. describes tags and the decoding strategy that are different from the claimed invention, it indicates that the terms "bit of binary code" or "binary coding" are recognized and understood by those skilled in the art.

The claims also recite the step of "performing an assay capable of indicating" the presence of a compound having a selected property of interest. The application provides once the chemical libraries are generated, a wide variety of chemical and biochemical assays to identify individual compounds eliciting a positive response, and such assays are known in the art. A receptor-ligand binding assay is provided as one such example. See pages 6 and 2, and the originally filed claims 11 to 13 of PCT/US98/10719. Accordingly, contrary to the Examiner's statement, the application does provide guidance as to assays that are capable of indicating the presence of a compound of interest in a combinatorial library.

The claims, as the Examiner pointed out, recite that the identity of the chemical compound is determined by optically interrogating the corresponding fluorophore tag, while the tag is bound to the solid support. The claims also state that the tag may be bound to the solid support directly, or to the component of the compound. Thus, the claims include a situation where the binding assay is performed after the compound is cleaved (i.e., when the tag is attached to the solid support and not to the component) as well as where the compound is bound to the solid support. In the assay involving the cleavage of the compound, the logical linkage between the solid support and the compound is maintained, for example, by maintaining the physical proximity between the solid support and the compound by preventing the compound from diffusing away.

Rejections Under 35 U.S.C. §102(b)

Claims 74-75, 79, 80-81, 83-84, 86-87, 92-93 were rejected under 35 U.S.C. §102(b) as

being anticipated by WO93/06121 to Dower et al ("Dower"). The Office Action alleged that Dower discloses a method of synthesizing a library of random oligomers on solid supports, in which an identifier tag is used to identifier the sequence of monomers in the oligomer, and screening the library for a compound having a selected property of interest. Applicants respectfully traverse the rejections.

Claims 98 to 128 are directed to a method of identifying a compound of interest from a library of compounds which utilizes a novel combination of an encoding and a decoding scheme. Specifically, the claimed method comprises preparation of a library of compound using a divide-couple-recombine strategy (DCR strategy) in which the identity of each of the component reacted with the solid support in generating a compound is identified by also attaching a spectrally distinguishable fluorophore tag uniquely associated with each component. The library is then screened for the presence of a compound having a selected property of interest. The identity of the compound of interest is determined by optically interrogating the set of the fluorophore tags bound to the solid support while the compound of interest was produced, and the interrogation is performed without physically isolating the beads of interest from other beads.

The encoding-decoding combination of the claimed method provides significant advantages. Specifically, because the beads of interest need not be isolated from other beads, and because the tags need not be cleaved from the bead for purposes of decoding (and hence compound identification) process, the claimed method is more efficient in terms of time and labor required for the identification step. Furthermore, by eliminating the requirement for physical isolation, the claimed method simplifies the implementation and automation of bead library screening and decoding See pages 3-4 of the Specification.

Dower does not anticipate the claimed invention, at least because it does not disclose the step of identifying the compound of interest from a library of compounds that does is carried out without removing the beads of interest from the mixture. In fact, Dower specifically teaches that

the compound identification requires that beads of interest be removed from the mixture to accomplish this identification step:

> Recovering and Decoding the Identifier Tag Information. When specific beads are isolated in a receptor screening experiment, the beads can be segregated individually by a number of means, including: infinite dilution, micromanipulation, or preferably, fluorescence activated cell sorting (FACS) . . . Once the desired beads have been isolated, one needs to identify the tag to ascertain the sequence of the oligomer on the bead.

See page 26, lines 9-17 of Dower.

The Examiner also pointed out this aspect of Dower in the Office Action, stating that Dower teaches that the library be screened to "isolate individual oligomers that bind to a receptor, or possess a desired property," and that the fluorescent beads are recovered from the positive wells" and removed and sorted by FACS. See pages 9 to 10 of the Office Action. Thus, by disclosing that the beads of interest must be isolated for purposes of identification, Dower provides a method of decoding that is more time and labor intensive than the claimed method.

In addition, Dower does not anticipate the claimed invention because it does not disclose a binary coding strategy using fluorophore dyes that are spectrally distinguishable by excitation wavelength, emission wavelength, excited-state lifetime or emission intensity. The identifier tag that is described in detail and referred to in Dower comprises an oligonucleotide, which must be isolated and sequenced to determine the identity of the corresponding compound. Although Dower also refers to an identifier tag in which fluorophores are used, it does not disclose a binary coding strategy using said dyes. Rather, it provides that the fluorophores may be photobleached or changed in some way to alter the spectral properties as a means of storing information. See page 20 of Dower.

In view of the foregoing, Applicants respectfully maintain that the claims are not

anticipated by Dower, and request that the rejections be reconsidered and withdrawn.

Rejections Under 35 U.S.C. §103

Claims 74-74, 79, 80-81, 83-84, 86-87, and 92-93 were rejected under 35 U.S.C. 103 as being unpatentable over U.S. Patent No. 5,968,736 to Still et al. ("Still"). It is alleged that Still et al. describes a method for generating a combinatorial library of compounds in which the identity of the compounds and the reaction history of the constituent components is recorded using identifiers, including radioisotopes, fluorescers, and halogens. The library is then screened for the presence of a compound of interest. Applicants respectfully traverse these rejections.

Still does not render obvious the claimed invention, at least because it does not teach or suggest that the identification of the compound of interest may be carried out without removing the beads of interest from the mixture and without cleaving the identifier tag from the beads for further analysis. Rather, as with Dower, Still teaches that the identification step be carried out by isolating the beads of interest from other beads, and by cleaving the tags from the beads for further off-line analysis. See column 6, lines 26 to 41; and column 17, lines 2 to 18. Still provides that the tag is attached to a cleavable linker, which is in turn attached to the solid support, such that the tag may be released from the solid support by cleaving the linker. See column 4, lines 8-25. It further addresses the critical role that the detachment of the tag plays in the method described therein:

> Importantly, the present method employs tags which are detachable from a ligand or compound synthesized also for the purpose of decoding. Such detachability allows the tags to be distinguished on more than one basis; in particular, they can be separated (e.g., on the basis of chromatographic retention time) and then analyzed (e.g., a second basis is a spectral property such as mass spectroscopy m/e, or electrophoricity). Having multiple bases for distinction allows the encoding of large amounts of information with a small number of tags.

See column 6, lines 26 to 35.

Accordingly, Still does not teach or suggest that a decoding of the identify of the compound of interest in a chemical library may be carried out without detaching the tags from the solid supports and without removing the beads of interest from other beads. The claimed invention, which teaches such a method, provides advantages that are not present in Still. By allowing a direct optical interrogation of the tags, the claimed method eliminates the segregation as well as tag cleaving and off-line analysis steps, thereby minimizing the time and labor associated with s.

In view of the foregoing reasons, Applicants respectfully maintain that the claims are patentable over Still.

Claims 74-77, 79-81, 83-84, 86-90, 92-93 and 95 are rejected under 35 U.S.C. 103 as being unpatentable over Dower in view of Metzeker et al. Applicants respectfully traverse these rejections.

Claims 98-128 are not rendered obvious by Dower, for the same reason as set forth in the above. To briefly reiterate, Dower does not teach or suggest the decoding of the tags without removing the beads of interest from the mixture, and Metzeker does not remedy this deficiency. In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of these rejections.

In view of the foregoing amendments and remarks, Applicants maintain that the application is in condition for allowance. An early and favorable action on the merits is earnestly solicited.

If the Examiner is of the view that there are any issues which remain pending after this Amendment, an interview is respectfully requested prior to issuance of any paper other than a

Notice of Allowance; and the Examiner is respectfully requested to contact the undersigned by telephone to arrange a mutually convenient time for the interview.

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Page 20, line 28, to page 21, line 7 of the Specification: Original Paragraph

One method of forming planar bead arrays is to rely on gravity-driven settling of beads from suspension to produce a (static) layer of beads or arrangement of bead clusters on a planar substrate. A second method employs dynamic planar bead arrays that are formed adjacent to planar surfaces and manipulated in-situ under external control, for example by Light-controlled Electrokinetic Assembly of Particles near Surfaces (LEAPS). LEAPS is a technology that provides the capability to form dynamic planar bead arrays in aqueous solution on cue and to place and maintain them in a designated area of a planar electrode, as set forth in the copending PCT application filed April 24, 1997, entitled "Light-Controlled Electrokinetic Assembly of Particles Near Surfaces," based on U.S. ~~Provisional Application Serial No. 60/016,642, filed April 25, 1996~~ Serial No. 09/171,550, which is incorporated by reference herein.